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Albert Lasker Award for Basic Medical Research, 2001

Press release

Mario Capecchi, Martin Evans and Oliver Smithies

This year's Lasker Basic Medical Research Award honors three scientists who developed a powerful technology that allows scientists to create animal models o human disease. With this technology, researchers have engineered mice with conditions such as atherosclerosis, cancer, high blood pressure, and cystic fibrosi allowing the study of many debilitating disorders. And the same technology is uncovering the secrets of normal biological processes as well, revealing, for exan how the nervous system develops or how immune cells collaborate to quash micr invaders.

This progress depends on the ability of researchers to manipulate the genetic material of mice with exquisite precision. Scientists can disable-or knock out-a g and they can also change its properties in more subtle ways. These procedures generate animals that carry specific genetic alterations, and recreate the underly cause of a human disorder or uncover the role of any gene of interest.

Inactivating a mouse gene takes two steps. In the first, scientists snip out its mi in a test tube using conventional tools of molecular biology. The challenge then i replace the intact, functional gene in the mouse chromosome with the modified version created in the test tube. This genetic swap requires the introduced DNA t find the corresponding DNA in the chromosome. Less than two decades ago, conventional wisdom held that this task was impossible in mammalian cells, and DNA could insert only at random sites.

At the time, knocking out a particular gene was about as successful as tossing a into a heap of spaghetti and hoping it hits a particular strand in a certain spot. Scientists could add DNA to mouse cells, but it landed in random places. They couldn't yet target DNA to a particular site in the chromosome-in other words, to specific gene. Today, hitting a bull's-eye is a standard maneuver.
By building on several decades of fundamental studies in mouse embryology and molecular genetics, Mario Capecchi, Martin Evans, and Oliver Smithies brought th work to fruition and delivered the technology of gene targeting in living mice to l around the world. Scientists can now create and breed mice with particular pathologies, study them systematically, evaluate the functions of genes in an int mammal, and dissect even the most complex processes.

How cancer helped

The seeds of this technology grew out of a bizarre form of cancer of the gonads, called a teratocarcinoma. Most tumors possess characteristics of their specific cel origin, but teratocarcinomas display features of many different tissues. Skin, mu hair, and even teeth compose these masses. Researchers showed in the 1960s a 1970s that this chaotic mixture of tissue types is all derived from an immature ty of cell with many potential fates, called an embryonic carcinoma-or EC-cell.

In this respect, EC cells from teratocarcinomas resemble embryonic stem (ES) ce from normal animals, which scientists knew existed, but could not isolate. ES cell develop soon after fertilization, and they too have not yet committed to any particular tissue type. A number of labs showed that EC and ES cells are close co in other ways as well. Early embryos turn into teratocarcinomas instead of mice i

they are implanted into sites in an adult mouse other than the uterus. And most importantly for the enterprise of gene targeting, either type of cell injected into v young embryos grows into normal parts of the fully developed mouse. The result "chimeric" animals carry some cells from their "normal" mother and father, and s cells from the mouse that donated the EC or ES cells.

In principle, if scientists could alter the DNA of a cell that would contribute to a li mouse, they could create an animal with any desired genetic change. The proces would involve altering the cell's DNA in a culture dish and generating a chimeric mouse that incorporates that cell's new genetic information into its sperm and eg But EC cells didn't lend themselves to this task. They contributed to most parts o mouse, but it proved difficult to produce animals with the EC DNA in egg or sperr an accomplishment that was essential to breed animals with the genetic change. cells seemed more promising, but they presented a different problem. Manipulati genes and then sorting through many cells to find the desired alterations wasn't possible with these cells because scientists couldn't grow them in the culture dish where such maneuvers would take place.

Martin Evans, then at the University of Cambridge and now at Cardiff University i the U.K., considered several explanations for the inability to culture ES cells from early embryo. Such cells could be rare, he reasoned, and they might not survive outside of the mother. Furthermore, they might exist for only a very short time a exact phase of embryonic development.

Evans zeroed in on the time period when he thought ES cells existed in the embr To increase the number of potential cells, he and his colleague Matt Kaufman del implantation of the early embryo into the mother's uterus. This procedure allowe embryos to accumulate cells at the right stage.

In the early 1980s, Evans and Kaufman harvested the early embryos, grew them culture dishes, and picked out cells that closely resembled EC cells. They had hit These cells formed teratocarcinomas when injected into mice. Furthermore they be maintained for long periods of time in culture and specialized magnificently w the petri dish. They possessed all the features that identified them as the sought after embryonic stem cells.

Evans had isolated the much-pursued multi-purpose cells. In principle, their DNA could be manipulated to create any mutation of interest. But how were scientists going to accomplish this task with the exquisite precision they desired? The only to manipulate an organism's DNA at the time was to integrate genes randomly. T ability to produce so-called transgenic mice has proved extraordinarily powerful i many ways, but because the newly introduced gene (transgene) adds to a chromosome at a random position, it leaves the resident copy of the gene intact. result, the transgene technique allows scientists to add genes; it does not permit them to subtract genes or to alter them at will.

Gene targeting

While Evans was tracking down embryonic stem cells, Mario Capecchi, at the University of Utah in Salt Lake City, and Oliver Smithies, first at the University of Wisconsin in Madison and later at the University of North Carolina in Chapel Hill, trying to target genes by a process called homologous recombination-"homologo because the incoming DNA sequence lines up with its twin target sequence in the chromosome, and "recombination" because the incoming and target molecules b and rejoin with each other. Depending on the technical details, the process repla one version of the gene with another or adds another copy of the gene in tandem 1982 Capecchi showed that mammalian cells contain efficient enzymatic machine for mediating homologous recombination between DNA molecules injected into th cell. With the thought of exploiting this machinery to carry out homologous recombination between newly added DNA and the corresponding chromosomal sequence Capecchi and Smithies had the bold idea that they could alter any gene the cell by replacing it with a modified version. Many scientists doubted that this notion would pan out. How could a unique incoming gene successfully sift throug vast amount of DNA in mammalian chromosomes and correctly home to the prop site? But Capecchi and Smithies persevered.

Smithies devised a laborious-but extremely sensitive-method to find cells in whic gene integration occurred at a chosen location. He aimed to detect such rare cell among the many more in which the gene would occur at random sites. The winni cell would contain a single piece of DNA that carried unique features of both the i gene and the resident gene-characteristics that had resided on two different molecules at the beginning of the experiment, but had become next-door neighb through homologous recombination.

Smithies sequentially divided a population of 4400 cells into smaller and smaller pools, tracking the ones that contained pieces of DNA with diagnostic features of the donor and recipient molecules. Eventually, he found a cell that carried the cri combination of DNA sequences on a single molecule, and published the work in 1 His discovery showed that specific planned modification of native genes was poss The DNA dart had found its corresponding sequence in the vast tangle of chromosomal DNA; he'd targeted a specific gene.

Capecchi took a different tack. First, his lab generated mammalian cells that contained insertions of a defective drug resistance gene. In a second step, the researchers introduced target DNA that carried a different defective version of th gene into the same cells. Homologous recombination between the two sequences could create an operational gene, and only cells in which the two defective versio recombined would resist the lethal effects of a toxic drug. This approach allowed scientists to easily find cells in which homologous recombination occurred, and h them work out experimental conditions that made this process occur more efficie

These advances were big wins-but the game wasn't over. How would scientists harness this capability to inactivate genes? And how would they extend the appr from cultured mammalian cells to the whole mouse.

Knocking out genes

Because the efficiency of gene targeting was low, the idea was to find the rare cultured ES cells that contain the new genetic alterations, and then implant those cells into early embryos. The resultant mice would breed to produce offspring tha harbored the genetic change in every cell.

By 1987, both Capecchi and Smithies had shown that they could target a native in ES cells. They chose the same gene, hprt, for practical reasons. Because of the peculiarities of the gene's function, the teams could isolate cells that contain defective or normal versions by exposing cells to different chemicals. This aspect hprt allowed them to find knockout cells and also cells in which a mutation in the gene had been corrected. These experiments established the paradigm of knocki out a gene.

But most genes do not share these special properties of hprt. Capecchi wanted t develop a system that would be of general use in altering genes. Random recombination was 1000 times more frequent than homologous recombination sc needed to figure out a way not only to identify cells that carried the new DNA, bu also to eradicate cells that carried it in the wrong site in the chromosome.

In 1988, Capecchi formulated a general strategy to enrich for cells in which the homologous targeting event had occurred. The scheme that he devised, now call the "positive-negative" method, not only enriches for recipient cells that have incorporated the DNA; it eliminates those that have allowed it to integrate at ran sites. Most importantly, this technique makes it possible to replace virtually any of interest.

Making designer mice

In the meantime, Evans had been pursuing mouse embryonic stem cell technolo developing its use as a way to make designer mice. He and his student Allan Bra and postdoctoral fellow Elizabeth Robertson had demonstrated that ES cells coul generate chimeric animals capable of transmitting their genetic material to offspr Furthermore, they had modified ES cells in culture dishes to create mice that wo breed to produce baby mice with the genetic alterations in every cell.

With this combination of Evans's accomplishments in ES cell technology and Capecchi's and Smithies's achievements in directed gene targeting, one could no dream of altering any single gene in ES cells growing in culture, and then creatin mouse with the genetic change in all of its cells. In 1989, four groups realized thi dream, each disabling a different gene.

A legacy

More than 4000 genetically engineered mice owe their existence to the technolo developed by Capecchi, Evans, Smithies, and their colleagues. In addition to kno out genes, the same method allows scientists to engineer precise changes in a particular gene. Insight into the processes to which these genes contribute is exploding as researchers assess the effects of the alterations, and pharmaceutica companies are using the resulting mouse models of disease to develop drugs. Refinements of the gene targeting technique are even allowing investigators to c a desired mutation in one particular tissue or at one particular time in the animal life. This ability allows scientists to study, for example, the effects of a gene in ar adult mouse that's required for embryonic development. They can allow the anim develop normally, and then inactivate the gene when desired.

Because genes influence nearly all biological phenomena, this technology is impa the analysis in fields as diverse as cancer, immunology, neurobiology, human ge disorders, endocrinology, and neurobiology. Capecchi, Evans, and Smithies have revolutionized the study of human health and disease.

Citation text by Evelyn Strauss, Ph.D.

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